October 27, 1997
VIA Facsimile: 919/541-0295

NTP Board of Scientific Counselors' Report on Carcinogens Subcommittee
c/o Dr. Larry G. Hart, Executive Secretary
NIEHS
Research Triangle Park NC

Re: RC Draft Background Document for TCDD

Dear Members of the Subcommittee:

As a cancer epidemiologist and an invited observer to the IARC working group evaluation of the carcinogenicity of dioxin, I have considerable interest in the resulting report and the use of that report by other organizations. It is in that context that I have been asked by the American Forest and Paper Association to review the document referenced above, as well as the "new" study on the Seveso cohort that was distributed with the document. You will find attached a copy of my comments on the draft document and the updated report on mortality from the Seveso cohort.

I hope that you find these comments to be helpful in your deliberations. In addition, I plan to attend the public hearing on this topic later this week and would be grateful for the opportunity to make a few remarks to the Subcommittee at that time. Thanks in advance for your consideration.

Sincerely,

Raymond S. Greenberg, MD, PhD
Charleston SC

Enclosures

Comments on:
Bertazzi et al., Dioxin Exposure and Cancer Risk.
***Epidemiol*, (in press)**

Raymond S. Greenberg, MD, PhD
Charleston SC

- **In this paper, a large number of potential cancer outcomes were examined, few of which revealed positive associations.**

  This paper included analyses that presented separate results stratified simultaneously by cancer type, zone (of exposure) and gender. There were 27 types of cancer for males (including all cancers combined) and 26 types of cancer for females. In addition, there were three exposure zones. Accordingly, there were (27 x 3) + (26 x 3) = 159 reported outcomes. If these were all independent, and dioxin exposure was not related to cancer mortality, one would still expect 8 results to be statistically significant at the 0.05 level (159 x .05). In fact, a total of 8 results were observed to be statistically significant at the 0.05 level. Accordingly, the findings reported here are entirely consistent with chance.

- **There was a lack of internal consistency in most of the reported findings, which was unlikely to have arisen from biological differences.**

  Most of the positive associations observed among males were not found among women and *vice versa*. For example, the authors cited an excess of rectal cancer deaths among males in zone B, with virtually no association seen among women. Among males in zone R, an excess of respiratory cancer deaths was reported for males, but there was an apparent deficit among females. An excess of deaths from leukemia among men was reported for zone B, but fewer than expected deaths were found for women. In zone B, women were reported to have an excess of deaths from multiple myeloma, but no such excess was found for males. In zone R, there was an apparent excess of deaths from soft tissue sarcomas among men, but no soft tissue sarcoma deaths were reported among women (with 1.5 expected).

  Although it is possible to speculate that biological differences between males and females might explain gender differences in the risks of certain cancers, such explanations seem unlikely for the particular cancer sites. None of the cancers in question is known or even suspected to be sex hormone-dependent. Interestingly, cancers that are known to be sex hormone-related, such as those involving the breast, ovaries, uterus, and prostate, did not reveal any excesses in mortality in this investigation. It is unlikely, therefore, that the gender differences observed in this study are biologically based. It is

more likely that the inconsistencies reflect either false-positive associations where the excesses were noted, or false negative results where associations were not observed. The likelihood of obtaining false negative results in a study is measured by the statistical power, which is directly related to the sample size, the frequency of the outcome and the magnitude of any true effect. For zones B and R, the present study had a sample size that was sufficiently large to detect moderate to strong associations for all cancers combined and for lung cancer. In that regard, it is worth noting that for both men and women, no excess was observed in either zone B or R for these outcomes. While one cannot rule out a very weak association from these results, these data do not support an association at the strength typically observed with cause-and-effect relationships (a relative risk of two or three).

- **The isolated positive associations did not reveal any clear dose-response relationship.**

  The most heavily exposed population was that residing in zone A. For males, there was a borderline statistically significant **deficit** of all cancer deaths combined, with less than half the number expected. Summing across gender, the observed number of all cancer deaths combined was 16, with an expectation of 23. For digestive cancer, one of those highlighted by the authors, the number of deaths among males in zone A was one-fifth of the expectation, a result that approached statistical significance. For soft tissue sarcomas, a cancer that has been associated with dioxin exposure in other settings, there was no evidence of any excess in either of the two most heavily exposed zones. Nevertheless, the authors chose to highlight in their abstract the small, non-statistically significant excess mortality that was observed only among males in zone R, the least contaminated area.

- **The findings were largely inconsistent with those from other studies on human populations heavily exposed to dioxin.**

  In its summary of the evidence concerning the potential carcinogenicity of dioxin among humans, the International Agency for Research on Cancer (IARC) working group found that the most consistent positive association was for all cancers combined. Less convincing evidence was found for site-specific cancers, such as lung cancer, non-Hodgkin lymphoma, and soft-tissue sarcoma. In contrast, the Bertazzi et al paper reported no excess of deaths from all cancers combined. Summing results across all three zones and both genders, the observed total number of cancer deaths was 1,176, with an expectation of 1,259.7 (Relative Risk = RR = 0.93). The total number of lung cancer deaths was 245, as compared with an expectation of 257.9 (RR = 0.95). For non-Hodgkin lymphoma, the observed total number of deaths was 20, with 21.7 expected (RR = 0.92). For soft tissue sarcoma, the

observed number of deaths was 4, with 3.97 expected (RR = 1).

- **The authors attempted to tie together disparate findings by aggregating them into broad organ system categories (e.g., digestive diseases), which ignore basic etiologic dissimilarities.**

  The authors refer to excesses of "digestive" cancers among women in zone A and after ten years of latency in zone B. For zone B, the authors also report more specific excesses of stomach cancer mortality among women and rectal cancer among men. The category of digestive cancers includes malignancies of any of the following organ sites: esophagus, stomach, colon, rectum, hepatobiliary tract, liver, pancreas, and other unspecified sites. Epidemiologically, cancers of these anatomic sites are quite distinct. For example, beverage alcohol consumption appears to be a risk factor for esophageal cancer and perhaps rectal and pancreatic cancer, but not for the other sites. Similarly, cigarette smoking is a risk factor for esophageal and stomach cancers, but not for the other sites. Infection by *Helicobacter pylori* appears to play an important role in the development of stomach cancer, but not in the other sites. All of the known epidemiology suggests that these anatomic sites have different and distinct risk factor profiles, and therefore, the usual and customary manner of investigating them is to treat them as unique outcomes. Linking isolated findings for different anatomic sites into a broad and ill-defined aggregate category may falsely imply consistency of results, but it makes little sense from an etiologic point of view.

- **The results of the latency analysis are inconsistent and only selectively presented.**

  For all cancers combined, the risk of death appeared to increase beyond 10 years among women, but not for men. Similarly, the mortality from "digestive" cancers appeared to increase after 10 years among women, but not among men. In fact, the only cancer site presented for which there was an increased risk of death with increased latency among men was rectal cancer, and no results were presented for this site for women. The authors presented latency analyses only for zone B and only for selected cancer sites. No statistics were presented to help judge whether or not chance was a likely explanation of the observed latency results. For most of the site-specific analyses presented, the numbers of observed deaths were small, and therefore, the resulting estimates of effect were highly unstable (as reflected by broad confidence intervals).

- **Alternative explanations for reported outcomes are not thoroughly explored.**

  For males in zone B, three pleural cancers were observed, with an

expectation of 0.6. An obvious question is whether these individuals had any exposure to asbestos, which is the principal known cause of mesothelioma. For such a small number of affected individuals, inquiry could have been made into their occupational histories at minimal effort and expense, and such information would have proven valuable in the interpretation of the present findings.

Comments on: RC Draft Background Document for TCDD

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- **Pg. RC-1, lines 17-18: "In the highly exposed industrial sub-cohorts, a causal relationship between TCDD exposure and mortality form all cancers combined was noted. . ."**

  The report of the IARC Working Group did not characterize the association as *causal.* In fact, the report states clearly that "While this relative risk does not appear likely to be explained by confounding, this possibility cannot be excluded" (p. 337). The report goes on to add that: "This lack of precedent for a multi-site carcinogen without particular sites predominating means that the epidemiological findings must be treated with caution" (p. 337). Finally, the report concluded that "there is *limited evidence* in humans for the carcinogenicity " of TCDD (p. 342). Thus, the association with all cancers combined was not deemed to be sufficient for causal inference.

- **Pg. RC-1, lines 19-21: "Increased risk for certain cancers was also reported in a new study of the Seveso, Italy, dioxin-exposed population (Bertazzi et al., 1998 [in press])."**

  The paper in question is not from a *new* study. Rather, as indicated subsequently in the document (page 3-1), this is an update of a cohort that has been followed since 1976, and about which reports have appeared multiple times in the peer-reviewed literature (see Bertazzi et al., *Am. J. Epidemiol,* 1989; **129**:1187-99, Bertazzi et al., *Organohalogen Compounds* 1996; **30**:294-6).

- **Pg RC-1, lines 21-23: "The additional findings were not considered in the IARC evaluation and further strengthen the association between dioxin-exposure and human cancer."**

  The 15-year follow-up results of Bertazzi et al., 1998 (in press) were available to the IARC Working Group. They were presented at an international dioxin meeting and reported in a peer-reviewed publication (Bertazzi et al., *Organohalogen Compounds* 1996; **30**:294-6). These findings are summarized in Table 33 of the IARC report (pp. 146-147) and in the corresponding text (p. 161). The only aspect of the new paper that was not cited in the IARC report was the subanalysis of the results by latency period. Because these latency results were not yet accepted by a peer-reviewed journal, the IARC Working Group felt that it was inappropriate to

include them in its report, and therefore, did not include the Seveso cohort in summary Table 38.

- **Pg. 3-2, lines 2-3: "In the largest and most heavily exposed German cohort, a dose-response relationship was noted for overall cancer mortality."**

  The dose-response relationship in question can be found in Table 39 (p. 194) of the IARC report. As noted in the IARC report: "This is largely the result of the high RR for the highest exposure group." Since there was not a smooth graded increase across the full range of exposure levels studied, it is inappropriate to use a linear test for trend, as was done by the authors of the paper in question. The test statistic resulting from a linear test for trend does not represent a valid estimate of the statistical significance of the observed pattern. The entire relationship was driven by a single outlying observation point. Moreover, only about 15 percent of this cohort had actual dioxin measurements; the doses of the remainder were imputed from job category and years of employment. Finally, the citation for this dose-response trend comes from an erratum, which is hardly reassuring about such a heavily emphasized finding.

- **Pg. 3-2, lines 6-8: "In its summary of the epidemiological evidence for the most highly exposed populations, the IARC Working Group identified a causal association between TCDD exposure and all cancer combined . . ."**

  As noted above, the IARC Working Group did not conclude that the epidemiological evidence supported a *causal* interpretation for the all cancer combined results. The report clearly concluded that confounding could not be excluded as a possible explanation (p. 337), and further suggested caution in any inference of causality given the absence of any strong site-specific associations. The IARC Working Group therefore concluded that there was *limited* (as opposed to sufficient) evidence in humans for carcinogenicity.